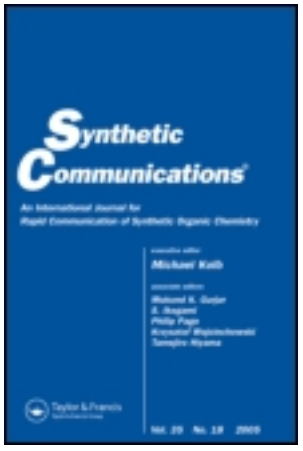

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Synthesis of Some New Tetrahydrobenzo[b]thiophene Derivatives and Tetrahydrobenzothienopyrimidine Derivatives Under Microwave Irradiation

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SYNTHESIS OF SOME NEW TETRAHYDROBENZO[b] THIOPHENE DERIVATIVES AND TETRAHYDROBENZO-THIENOPYRIMIDINE DERIVATIVES UNDER MICROWAVE IRRADIATION

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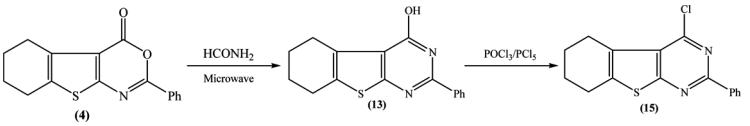
GRAPHICAL ABSTRACT



Abstract *2-Phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d][1,3]oxazin-4-one (**4**) was reacted with either aliphatic or aromatic primary amines such as benzylamine, cyclohexylamine, p-toluidine, and/or p-anisidine to give carboxamide derivatives **5a–d**, respectively. A bifunctional nucleophile such as ethanolamine was also reacted with **4**, giving the carboxamide derivative **5e**. Aminolysis of **4** with secondary amines such as piperidine and/or morpholine afforded the benzamide derivatives **6a** and/or **6b**, respectively. Fusion of **4** with hydrazine hydrate yielded the pyrimidine derivative **7** and carbohydrazide derivative **8**. Thiation of **4** with phosphorous pentasulfide gave thienothiazine derivative **9**, which reacted with benzylamine to give the pyrimidine derivative **10**. Carbon nucleophiles such as ethyl cyanoacetate and/or malononitrile were subjected to react with **4** to give oxopropanoate **11** and/or oxopropanoic acid **12** derivatives, respectively. Microwave irradiation of **4** and formamide yielded the pyrimidinone derivative **13**, which were subjected to react with phosphorous pentasulfide, a mixture of phosphorous oxychloride and phosphorous pentachloride and/or methyl iodide, to give **14, 15**, and/or **16**, respectively.*

Keywords Microwave; tetrahydrobenzothiophene; tetrahydrothienopyrimidine

INTRODUCTION

The utility of microwaves in heterocyclic synthesis is now receiving considerable attention.[1–4] As a part of a recent project aiming to explore potential utility of microwaves as an energy source for heterocyclic synthesis, we report here on

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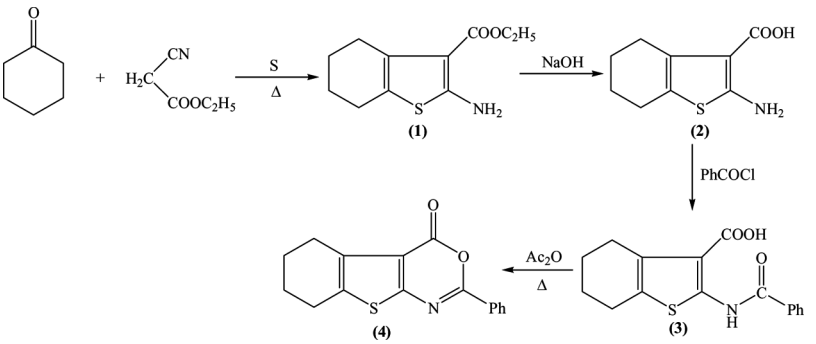
synthesis of new thienopyrimidines and tetrahydrobenzothiophene derivatives of expected biological activities, where a large number of thienopyrimidines were reported in literature as virucides, bactericides, fungicides, acaricides, and insecticides[5,6] as well as having anticancer, antiviral, antitumor, anti-inflammatory, antihistaminic, activities, and analgesic.[7–15] Also, a large number of tetrahydrobenzothieno derivatives were reported as anticancer, antibacterial, antimicrobial, and antifungal agents.[16,17] Tetrahydrobenzothiophene derivatives were reported also as inhibitors of hepatitis C virus NS5B polymerase.[18] The therapeutic importance of thienopyrimidines as well as tetrahydrobenzothiophene derivatives prompted us to construct several analogs by exotic combinations of groups and active moieties.

RESULTS AND DISCUSSION

The key starting material, 2-phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d][1,3]oxazine-4-one[19] **(4),** has been obtained in fair yield via the cyclization of 4,5,6,7-tetrahydrobenzothiophene-2-benzoylamino-3-carboxylic acid (**3**) with freshly distilled acetic anhydride (Scheme 1). Benzothiophene derivative (**3**) was obtained by benzoylation of 4,5,6,7-tetrahydrobenzothiophen-2-amino-3-carboxylic acid (**2**).[20] It was found that **2** was obtained upon alkaline hydrolysis of 4,5,6,7-tetrahydrobenzo-thiophen-2-amino-3-ethyl carboxylate (**1**),[21] which was prepared via Gewald reaction of cyclohexanone and ethyl cyanoacetate in the presence of sulfur[22] (Scheme 1).

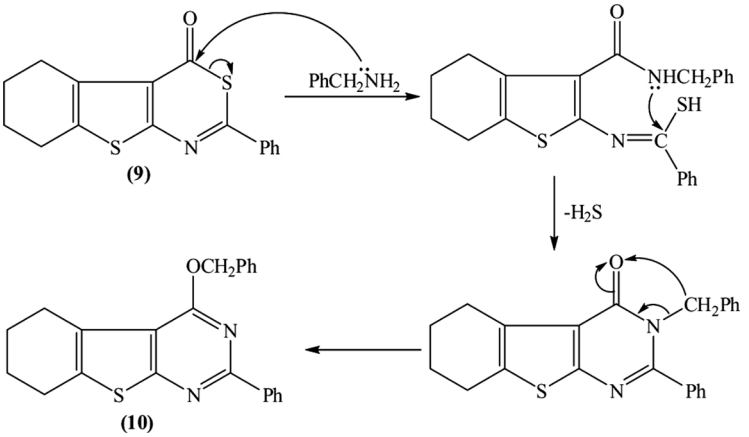
The structure of compound **4** was established by elemental analysis as well as spectral data [infrared (IR), mass (MS), ^{1}H NMR] and chemically via aminolysis under microwave irradiation with either aliphatic or aromatic primary amines such as benzylamine, cyclohexylamine, p-toluidine, and/or p-anisidine to give the corresponding carboxamide derivatives **5a–d**, respectively (Scheme 2). Bifunctional nucleophiles such as ethanolamine also reacted with **4** under microwave irradiation to give 2-benzamido-N-(2-hydroxyethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**5e**). Secondary amines such as piperidine and/or morpholine also reacted with **4** under microwave irradiation, giving N-[3-(piperidine-1-carbonyl)-4,5,



Scheme 1. Synthesis of 2-phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d][1,3]oxazine-4-one (**4**).

6,7-tetrahydrobenzo[b]-thiophene-2-yl]benzamide (**6a**) and/or N-[3-(morpholine-4-carbonyl)-4,5,6,7-tetrahydro-benzo[b]-thiophene-2-yl]benzamide (**6b**). Unfortunately, hydrazinolysis of **4** with hydrazine hydrate under microwave irradiation gave unreacted product, whereas when **4** was fused with hydrazine hydrate in an electro-mental instrument, 2-phenyl-3-amino-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d] pyrimidin-4-one (**7**) and 2-benzamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbo-hydrazide (**8**) were obtained.

Alternatively, treatment of oxazinone derivative (**4**) with phosphorous pentasulfide under microwave irradiation yielded 2-phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d][1,3]-thiazine-4-one (**9**), which upon aminolysis by benzylamine under microwave irradiation afforded the pyrimidine derivative (**10**) according to the following mechanism:

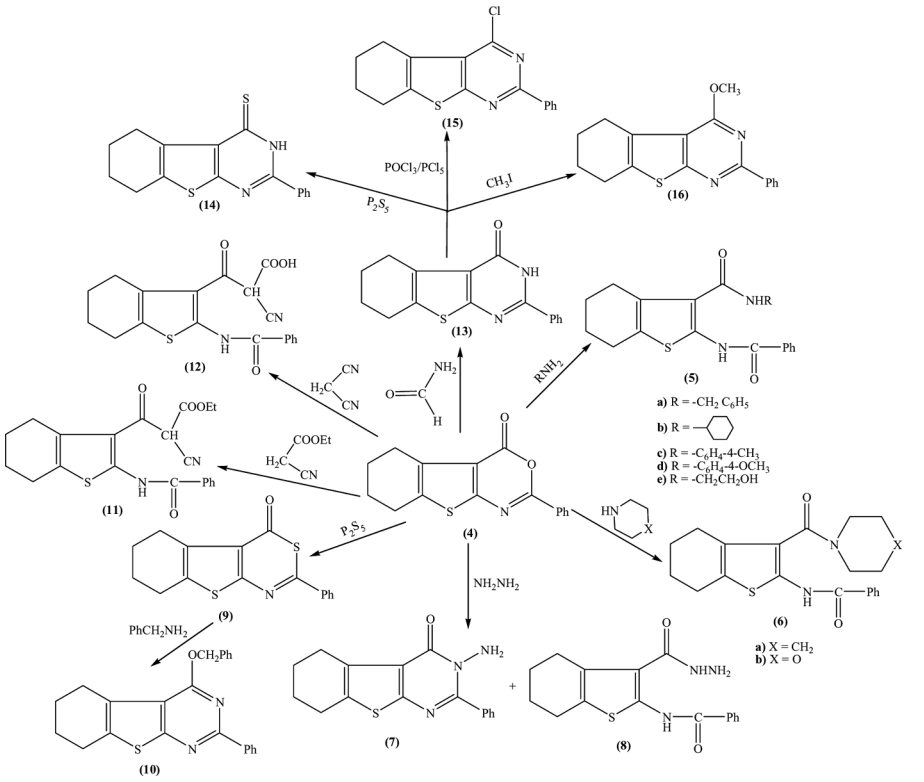


(9) (10)

Microwave irradiation of oxazinone derivative (**4**) with carbon nucleophiles such as ethyl cyanoacetate in ethoxide as a catalytic base afforded ethyl-3-(2-benzamido-4,5,6,7-tetraydrobenzo[b]thiophene-3-yl)-2-cyano-3-oxopropanoate (**11**) in fairly good yield. On the other hand, no product was formed upon reaction of **4** with malononitrile under microwave irradiation. Instead, reflux of **4** with an ethanolic solution of malononitrile in the presence of sodium ethoxide as a catalytic base gave 3-(2-benzamido-4,5,6,7-tetra-hydrobenzo[b]thiophen-3-yl)-2-cyano-3-oxopropanoic acid (**12**).

Treatment of oxazinone derivative (**4**) with formamide under microwave irradiation yielded 2-phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d]pyrimidine-4-(3H)-one (**13**), whose structure was confirmed by elemental analysis as well as spectral data. Furthermore, chemical proofs were achieved via the following:

(i) Microwave irradiation of **13** with phosphorous pentasulfide, which gave 2-phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d]pyrimidine-4-(3H)-thione (**14**) in quantitative good yield.
(ii) Chlorination of **13** with a mixture of phosphorous oxychloride and phosphorous pentachloride under heat in water bath for a long time, which afforded 2-phenyl-4-chloro-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**15**).



Scheme 2. Reactions of benzothieno[2,3-d][1,3]oxazine-4-one **4** with nitrogen and carbon nucleophiles.

(iii) Alkylation of **13** by reflux with methyl iodide in potassium carbonate as a catalytic base, which afforded the expected methoxypyrimidine derivative (**16**) (Scheme 2).

EXPERIMENTAL

Melting points were measured on an electrothermal melting-point apparatus, and elemental analysis was carried out at the Microanalytical Unit, Cairo University, Giza, Egypt. IR spectra were measured on a Unicam SP-1200 spectrometer using the KBr Wafer technique. ^{1}H NMR spectra were measured in dimethylsulfoxide (DMSO-d_6) or $CDCl_3$ on a Varian Plus instrument (300 MHz). MS were determined on a HP model MS-S988 at electron energy 70 eV.

4,5,6,7-Tetrahydrobenzothiophene-2-benzoylamino-3-carboxylic Acid (3)

A mixture of 4,5,6,7-tetrahydrobenzo[b]thiophene-2-amino-3-carboxylic acid (**2**) (0.01 mol) in dry pyridine (30 ml) and benzoyl chloride (0.02 mol) was stirred for 1 h in an ice bath. After cooling, the reaction mixture was acidified with ice-cold hydrochloric acid. The solid formed after complete acidification was collected and recrystallized to give **3**.

2-Phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d][1,3]oxazine-4-one (4)

A mixture of **3** (0.01 mol) and acetic anhydride (10 ml) was heated on a water bath for 5 h. The solid formed after removal of excess acetic anhydride was triturated with petroleum ether 40–60 °C and recrystallized from petroleum ether 80–100 °C to give **4** as yellow crystals; mp 138–140 °C, yield: 40%. IR (cm^{-1}): 1750 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 8.28–8.25 (2d, 2H), 7.59–7.49 (m, 3H), 2.99–2.95 (t, 2H), 2.82–2.79 (t, 2H), 1.93–1.87 (m, 4H). MS (*m/z*), %: 283 (M^+, 11.3), 255 (3.7), 105 (78.8), 77 (100). Anal. calcd. for $C_{16}H_{13}NO_2S$ (283.35): C, 67.82; H, 4.62; N, 4.94. Found: C, 67.84; H, 4.61; N, 4.93.

2-Benzamido-N-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (5a)

A mixture of **4** (0.01 mol) and benzylamine (0.01 mol) was exposed to microwaves at 600 W for 3 min, and after cooling the reaction mixture was treated with ice-cold hydrochloric acid. The solid mass was filtered and recrystallized from toluene to give **5a** as colorless crystals; mp 190–192 °C, yield: 80%. IR (cm^{-1}): 3342, 3242 (ν_{NH}), 1631.5 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 13.23 (s, 1H), 8.07–8.04 (d, 2H), 7.57–7.32 (m, 8H), 6.29 (s, 1H), 4.69–4.68 (d, 2H), 2.73–2.71 (m, 4H), 1.86–1.84 (m, 4H). MS (*m/z*), %: 390 (M^+, 6.3), 285 (1.7), 105 (100), 77 (74.4). Anal. calcd. for $C_{23}H_{22}N_2O_2S$ (390.50): C, 70.74; H, 5.68; N, 7.17. Found: C, 70.76; H, 5.67; N, 7.16.

2-Benzamido-N-cyclohexyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (5b)

A mixture of **4** (0.01 mol) and cyclohexylamine (0.01 mol) was exposed to microwaves at 900 W for 5 min. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid was filtered and recrystallized from toluene to give **5b** as colorless crystals; mp 244–46 °C, yield: 75%. IR (cm^{-1}): 3345 (ν_{NH}), 1670 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 13.19 (s, 1H), 8.06–8.03 (2d, 2H), 7.56–7.48 (m, 3H), 5.94–5.91 (br, 1H), 4.06–4.03 (m, 1H), 2.75–2.72 (m, 4H), 2.06–1.35 (m, 14H). MS (*m/z*), %: 382 (M^+, 18), 284 (8.3), 179 (6.6), 105 (100), 77 (71.2). Anal. calcd. for $C_{22}H_{26}N_2O_2S$ (382.52): C, 69.08; H, 6.85; N, 7.32. Found: C, 69.06; H, 6.84; N, 7.31.

2-Benzamido-N-p-tolyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (5c)

A mixture of **4** (0.01 mol) and *p*-toluidine (0.02 mol) was exposed to microwaves at 900 W. for 5 min. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid was filtered and recrystallized from petroleum ether 60–80 °C to give **5c** as colorless crystals; mp 198–200 °C, yield: 70%. IR (cm^{-1}): 3258, 3113.5 (ν_{NH}), 1640 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 13.03 (s, 1H), 8.06–8.03 (2d, 2H), 7.64–7.20 (m, 8H), 2.91–2.78 (2t, 4H), 2.37 (s, 3H), 1.93–1.92 (m, 4H). MS

(*m*/*z*), %: 390 (M^+, 8.1), 285 (2.7), 284 (10.7), 107 (100), 105 (80.4). Anal. calcd. for $C_{23}H_{22}N_2O_2S$ (390.50): C, 70.74; H, 5.68; N, 7.17. Found: C, 70.76; H, 5.68; N, 7.16.

2-Benzamido-N-(4-methoxylphenyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxamide (5d)

A mixture of **4** (0.01 mol) and *p*-anisidine (0.02 mol) was exposed to microwaves at 900 W for 10 min. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid mass was filtered and recrystallized from toluene to give **5d** as colorless crystals; mp 214–216 °C, yield: 80%. IR (cm^{-1}): 3372.5, 3267 (ν_{NH}), 1671 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 13.04 (s, 1H), 8.06–8.03 (d, 2H), 7.60–7.46 (m, 6H), 6.96–6.93 (d, 2H), 3.84 (s, 3H), 2.89–2.88 (t, 2H), 2.79–2.75 (t, 2H), 1.92–1.88 (m, 4H). MS (*m*/*z*), %: 406 (M^+, 6.6), 284 (10.9), 123 (100), 105 (57). Anal. calcd. for $C_{23}H_{22}N_2O_3S$ (406.50): C, 67.96; H, 5.46; N, 6.89. Found: C, 67.97; H, 5.46; N, 6.88.

2-Benzamido-N-(2-hydroxyethyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxamide (5e)

A mixture of **4** (0.01 mol) and ethanolamine (0.02 mol) was exposed to microwaves at 600 W for 3 min. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid was filtered and recrystallized from toluene to give **5e** as yellow crystals; mp 192–194 °C, yield: 75%. IR (cm^{-1}): 3484.7, 3448 (ν_{NH}), 1637 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 13.74 (s, 1H), 7.91–7.88 (2d, 2H), 7.68–7.60 (m, 3H), 7.30 (br, 1H), 4.79–4.76 (t, 2H), 3.58–3.56 (t, 2H), 3.54 (s, 1H), 2.75–2.67 (2 t, 4H), 1.77 (m, 4H). MS (*m*/*z*), %: 344 (M^+, 11.6), 284 (3.9), 105 (100), 77 (94.4). Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (344.43): C, 62.77; H, 5.85; N, 8.13. Found: C, 62.78; H, 5.86; N, 8.14.

N-[3-(Piperidine-1-carbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-yl]benzamide (6a)

A mixture of **4** (0.01 mol) and piperidine (0.02 mol) was exposed to microwaves at 900 W for 5 min. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid was filtered and recrystallized from petroleum ether 80–100 °C to give **6a** as colorless crystals; mp 180–182 °C, yield: 50%. IR (cm^{-1}): 3188.7 (ν_{NH}), 1660 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 10.12 (s, 1H), 7.94–7.91 (2d, 2H), 7.56–7.49 (m, 3H), 3.8–2.64 (2 t, 4H), 2.74–2.72 (t, 2H), 2.50–2.48 (t, 2H), 1.87–1.62 (m, 10H). MS (*m*/*z*), %: 368 (M^+, 11.4), 284 (10.8), 105 (100), 84 (44.4). Anal. calcd. for $C_{21}H_{24}N_2O_2S$ (368.49): C, 68.45; H, 6.56; N, 7.60. Found: C, 68.47; H, 6.55; N, 7.60.

N-[3-(Morpholine-4-carbonyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-2-yl]-benzamide (6b)

A mixture of **4** (0.01 mol) and morpholine (0.02 mol) was exposed to microwaves at 600 W for 5 min. After cooling, the reaction mixture was poured on ice-cold

hydrochloric acid, and then the solid was filtered and recrystallized from toluene to give **6b** as colorless crystals; mp 254–256 °C, yield: 90%. IR (cm^{-1}): 3221.5, 3195.5 (ν_{NH}), 1662 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 10.75 (s, 1H), 7.93–7.92 (2d, 2H), 7.88–7.51 (m, 3H), 3.62–3.50 (m, 8H), 2.67–2.40 (2 t, 4H), 1.79–1.71 (m, 4H). MS (*m/z*), %: 284 ($M^+ - 86$, 3.9), 105 (16.9), 86 (14.3), 77 (100). Anal. calcd. for $C_{20}H_{22}N_2O_3S$ (370.47): C, 64.84; H, 5.99; N, 7.56. Found: C, 64.85; H, 5.98; N, 7.58.

2-Phenyl-3-amino-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d]pyrimidin-4-one (7) and 2-Benzamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbohydrazide (8)

A mixture of **4** (0.01 mol) and hydrazine hydrate (0.01 mol) was heated in an electrothermal instrument at 100–110 °C. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the product mass was filtered and recrystallized to give **7** and **8**.

Compound 7. Recrystallized from petroleum ether 60–80 °C as colorless crystals; mp 114–116 °C, yield: 30%. IR (cm^{-1}): 3287, 3212 (ν_{NH}), 1657.5 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 7.94–7.92 (2d, 2H), 7.87–7.50 (m, 3H), 4.08–4.05 (m, 2H), 2.72–2.67 (2t, 4H), 1.77–1.75 (m, 4H). MS (*m/z*), %: 297 (M^+, 50.4), 281 (33.1), 269 (3.6), 150 (5.2), 103 (10.3), 77 (100). Anal. calcd. for $C_{16}H_{15}N_3OS$ (297.37): C, 64.62; H, 5.08; N, 14.13. Found: C, 64.61; H, 5.08; N, 14.11.

Compound 8. Recrystallized from ethanol as yellow crystals; mp 203–205 °C, yield: 60%. IR (cm^{-1}): 3356.5, 3238 (ν_{NH}), 1655.6, 1626.6 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 12.32 (s, 1H), 8.87 (s, 1H), 7.92–7.89 (2d, 2H), 7.68–7.58 (m, 3H), 4.70 (br, 2H), 2.71–2.66 (2t, 4H), 1.75–1.73 (m, 4H). MS (*m/z*), %: 284 ($M^+ - 31$, 3.5), 180 (8.9), 105 (100), 77 (66.5). Anal. calcd. for $C_{16}H_{17}N_3O_2S$ (315.39): C, 60.93; H, 5.43; N, 13.32. Found: C, 60.94; H, 5.44; N, 13.30.

2-Phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d][1,3]thiazin-4-one (9)

A mixture of **4** (0.01 mol) and phosphorus pentasulphide (0.01 mol) was exposed to microwaves at 900 W for 2.5 min. The reaction mixture was triturated with boiling water, collected, and recrystallized from petroleum ether 60–80 °C to give **9** as red crystals; mp 117–119 °C, yield: 70%. IR (cm^{-1}): 1749 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 8.25–8.23 (2d, 2H), 7.55–7.44 (m, 3H), 2.98–2.94 (t, 2H), 2.80–2.77 (t, 2H), 1.90–1.84 (m, 4H). MS (*m/z*), %: 299 (M^+, 4.9), 283 (30.3), 255 (9.8), 105 (78.4), 77 (100). Anal. calcd. for $C_{16}H_{13}NOS_2$ (299.41): C, 64.18; H, 4.38; N, 4.68. Found: C, 64.20; H, 4.39; N, 4.67.

2-Phenyl-4-benzyloxy-5,6,7,8-tetrahydrobenzothieno[2,3-d] pyrimidine (10)

A mixture of **9** (0.01 mol) and benzylamine (0.01 mol) was exposed to microwaves at 900 W for 6 min. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid was filtered and recrystallized from petroleum

ether 40–60 °C to give **10** as orange crystals; mp 140–142 °C, yield: 10%. IR (cm^{-1}): no bands for NH or CO. ^1H NMR (δ in ppm): 8.03–8.01 (2d, 2H), 7.54–7.32 (m, 8H), 4.86 (s, 2H), 3.29 (t, 2H), 2.86 (t, 2H), 1.91–1.55 (m, 4H). MS (*m/z*), %: 372 (M^+, 6.8), 265 (9.8), 107 (53), 91 (100), 77 (50.8). Anal. calcd. for $C_{23}H_{20}N_2OS$ (372.48): C, 74.16; H, 5.41; N, 7.52. Found: C, 74.18; H, 5.40; N, 7.50.

Ethyl-3-(2-benzamido-4,5,6,7-tetraydrobenzo[b]thiophene-3-yl)-2-cyano-3-oxo-propanoate (11)

A mixture of **4** (0.01 mol) and ethyl cyanoacetate (0.01 mol) in the presence of sodium ethoxide was exposed to microwaves at 900 W for 3 min. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid was filtered and recrystallized from petroleum ether 80–100 °C to give **11** as yellow crystals; mp 176–178 °C, yield: 20%. IR (cm^{-1}): 3294 (ν_{NH}), 1677, 1647 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 14.43 (s, 1H), 9.28 (s, 1H), 7.92–7.88 (2d, 2H), 7.60–7.53 (m, 3H), 4.48–4.43 (q, 2H), 2.77–2.73 (2t, 4H), 1.92–1.89 (t, 2H), 1.81–1.79 (t, 2H), 1.44–1.42 (t, 3H). MS (*m/z*), %: 396 (M^+, 13.6), 350 (22), 291 (5.4), 105 (100), 77 (53.4). Anal. calcd. for $C_{21}H_{20}N_2O_4S$ (396.46): C, 63.62; H, 5.08; N, 7.07. Found: C, 63.60; H, 5.06; N, 7.08.

3-(2-Benzamido-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-2-cyano-3-oxopropanoic Acid (12)

A mixture of **4** (0.01 mol) and malononitrile (0.02 mol) in ethanol (50 ml) was refluxed in the presence of sodium ethoxide (0.01 mol) for 8 h. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid was filtered and recrystallized from toluene to give **12** as brown crystals; mp 184–186 °C, yield: 30%. IR (cm^{-1}): 3243.7 (ν_{NH}), 1668, 1636 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 12.02 (s, 1H), 8.02–7.98 (2d, 2H), 7.63–7.50 (m, 3H), 2.88–2.71 (2t, 4H), 1.89–1.84 (m, 4H). MS (*m/z*), %: 368 (M^+, 0.9), 179 (32.03), 105 (100), 77 (10.8). Anal. calcd. for $C_{19}H_{16}N_2O_4S$ (368.41): C, 61.94; H, 4.38; N, 7.60. Found: C, 61.96; H, 4.36; N, 7.60.

2-Phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d]pyrimidine-4-(3H)-one (13)

A mixture of **4** (0.01 mol) and formamide (0.04 mol) was exposed to microwaves at 900 W for 5 min. After cooling, the reaction mixture was poured on ice-cold hydrochloric acid, and then the solid mass was filtered and recrystallized from toluene to give **13** as colorless crystals; mp 200–202 °C, yield: 90%. IR (cm^{-1}): 3395 (ν_{NH}), 1651 cm^{-1} (ν_{CO}). ^1H NMR (δ in ppm): 10.75 (s, 1H), 7.92–7.89 (2d, 2H), 7.64–7.51 (m, 3H), 2.66–2.64 (t, 2H), 2.48–2.40 (t, 2H), 1.79–1.71 (m, 4H). MS (*m/z*), %: 282 (M^+, 13.1), 179 (14.8), 105 (42.6), 104 (13.1), 77 (100). Anal. calcd. for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92. Found: C, 68.05; H, 4.99; N, 9.91.

2-Phenyl-5,6,7,8-tetrahydro-4H-benzothieno[2,3-d]pyrimidine-4-(3H)-thione (14)

A mixture of **13** (0.01 mol) and phosphorus pentasulphide (0.02 mol) was exposed to microwaves at 900 W for 10 min. After cooling, the reaction mixture was triturated with boiling water, collected, and recrystallized from toluene to give **14** as orange crystals; mp 286–288 °C, yield: 30%. IR (cm^{-1}): 3100 (ν_{NH}). ^1H NMR (δ in ppm): 12.48 (s, 1H), 8.14–8.10 (2d, 2H), 7.59–7.49 (m, 5H), 2.93–2.91 (t, 2H), 2.76–2.74 (t, 2H), 1.81–1.79 (m, 4H). MS (*m/z*), %: 298 (M^+, 13.4), 296 (100), 265 (9.8), 77 (86.6). Anal. calcd. for $C_{16}H_{14}N_2S_2$(298.43): C, 64.39; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.72; N, 9.37.

2-Phenyl-4-chloro-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (15)

A mixture of **13** (0.01 mol) and phosphorus oxychloride (10 ml) in the presence of phosphorus pentachloride (1 g) was heated on a water bath for 18 h. After cooling, the reaction mixture was poured on crushed ice. The solid was filtered and recrystallized from petroleum ether 80–100 °C to give **15** as yellow crystals; mp 154–156 °C, yield: 20%. IR (cm^{-1}): no bands for NH or CO. ^1H NMR (δ in ppm): 8.51–8.47 (2d, 2H), 7.52–7.47 (m, 3H), 3.14–3.12 (t, 2H), 2.89–2.87 (t, 2H), 1.96–1.92 (m, 4H). MS (*m/z*), %: 302 (M + 2, 19.68), 300 (M^+, 52.7), 265 (7.7), 103 (66.2), 77 (100). Anal. calcd. for $C_{16}H_{13}ClN_2S$ (300.81): C, 63.89; H, 4.36; N, 9.31. Found: C, 63.90; H, 4.35; N, 9.30.

2-Phenyl-4-methoxy-5,6,7,8-tetrahydrobenzothieno Pyrimidine (16)

A mixture of **13** (0.01 mol) and methyl iodide (0.02 mol) in the presence of anhydrous K_2CO_3 (2 g) in dry acetone (20 ml) was refluxed on a water bath for 20 h. The reaction mixture was filtered to separate K_2CO_3, and the solvent was evaporated. The solid was recrystallized from ethanol to give **16** as colorless crystals; mp 158–160 °C, yield: 30%. IR (cm^{-1}): no bands for NH or CO. ^1H NMR (δ in ppm): 8.44–8.38 (2d, 2H), 7.55–7.48 (m, 3H), 4.07 (s, 3H), 2.78–2.49 (2t, 4H), 1.77–1.73 (m, 4H). MS (*m/z*), %: 296 (M^+, 100), 295 (21.7), 281 (15.7), 103 (28.6), 77 (73.1). Anal. calcd. for $C_{17}H_{16}N_2OS$ (296.39): C, 68.89; H, 5.44; N, 9.45. Found: C, 68.88; H, 5.43; N, 9.45.

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